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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,440	02/05/2004	Michal Daniely	26003	3178

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/29/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,440	DANIELY ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *72,73,82,84,87,89,91 and 93* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *72, 73, 82, 84, 87, 89, 91 and 93* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed November 7, 2011, is acknowledged and has been entered. Claim 72 has been amended.

2. Claims 72, 73, 82, 84, 87, 89, 91 and 93 are pending in the application and are under examination.

Grounds of Objection and Rejection Withdrawn

3. Applicant's amendments filed November 7, 2011, have obviated or rendered moot the grounds of rejection set forth in the previous Office action July 6, 2011.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 72, 73, 82, 87, 89, 91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bubendorf et al (Am J Clin Pathol., 116:79-86, 2001, of record), in view of Skacel et al (Anal Quant Cytol Histol, 23(6): 381-387, 2001, of record) and in view of Brown (Urol. Clin. NA., 27(1):25-37, 2000, of record).

As amended, the claims herein recite methods comprising:

(a) staining nucleated cells of a voided urine sample using a stain selected from the group consisting of May-Grunwald-Giemsa, Giemsa, Papanicolau and Hematoxylin-Eosin to thereby obtain stained nucleated cells;

(b) imaging said stained nucleated cells resultant of steps (a) so as to obtain images of said stained nucleated cells, and;

(c) analyzing a nucleus to cytoplasm ratio in transitional epithelial cells by said stain in said images of step (b) and identifying a single cell having a morphological abnormality which comprises a high nucleus to cytoplasm (N/C) ratio as compared to a transitional epithelial cell with a normal morphology, said morphological abnormality indicates that said single cell is suspicious as being a transitional cell carcinoma (TCC) cell, and subsequently;

(d) de-staining said stain of step (a) and subsequently;

(e) staining said stained nucleated cells resultant of step (a) using fluorescent in situ hybridization (FISH) to thereby obtain stained nucleated cells stained with FISH, and; subsequently;

(f) imaging said nucleated cells stained with FISH resultant of step (e) so as to obtain images of said nucleated cells stained with FISH; and subsequently;

(g) identifying by said FISH in said images of step (f) a chromosomal abnormality in the same said single cell suspicious as being said transitional cell carcinoma (TCC) cell wherein said chromosomal abnormality indicates that said single cell is a transitional cell carcinoma (TCC) cell from a bladder cancer or kidney cancer; (see claims 72 and 82)

or methods comprising:

(a) obtaining a voided urine sample from the subject;

(b) identifying transitional cell carcinoma cells according to the method of claim 72; (see claim 73). Claim 87 further recites analyzing said transitional epithelial cells for a morphological abnormality selected from an enlarged nucleus, a considerable dark appearance of a cell or an irregular nuclear border as compared to a transitional epithelial cell with a normal morphology. Claims 89 and 91 are further drawn to said chromosomal abnormality being a polyploidy of chromosome 3, chromosome 7, chromosome 17 or loss of 9p21 locus. Claim 93 further recites that said nucleated cells of the voided urine sample are cyto-centrifuged at a cell density of 300-500 cells per mm^2 prior to step (a).

Bubendorf et al teach methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a voided urine sample comprising:

obtaining a voided urine sample from a subject

staining nucleated cells of the sample with DAPI and FISH probes from chromosomes 3, 7, 17 and 9p21 to obtain stained nucleated cells;

imaging said nucleated cells stained with DAPI and FISH so as to obtain images of said cells; and subsequently;

identifying in said images single target cells with morphological abnormalities like large nuclear size or irregular nuclear shape and then enumerating FISH signals on

these same single cells staining to identify transitional cell carcinoma cells from bladder cancers.

(see entire document, e.g., page 80, Materials and Methods, page 81, left column and Tables 2 and 3).

Bubendorf et al also teach methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a voided urine sample comprising:

obtaining a voided urine sample from a subject

staining nucleated cells of the sample with Papincolaou to obtain stained nucleated cells;

imaging the stained nucleated cells, and;

identifying in the images cells having a morphological abnormality (see page 80, Materials and Methods)

Bubendorf et al do not expressly teach destaining cells that have been stained with Papanicolau before using FISH stains and that transitional cell carcinoma cells can be identified by a high nucleus to cytoplasm (N/C) ratio.

These deficiencies are made up for in the teachings of Skacel et al and Brown.

Skacel et al teach staining nucleated cells of a voided urine sample with Papincolaou to obtain stained nucleated cells;

imaging the stained nucleated cells,

identifying in the images cells having a morphological abnormality,

de-staining the Papanicolau stain;

staining the resultant destained cells using fluorescent in situ hybridization (FISH) to obtain stained nucleated cells stained with FISH probes from chromosomes 3, 7, 17 and 9p21 to obtain stained nucleated cells, and

imaging said nucleated cells stained with FISH to obtain images of said nucleated cells stained with FISH; and subsequently;

identifying by said FISH in said images a chromosomal abnormality in the cells which indicates that the cell is a transitional cell carcinoma (TCC) cell from a bladder cancer (see entire document, e.g., 382, right column and pages 383 and 384).

Brown teaches that other morphological abnormalities that identify transitional cells as suspicious as transitional carcinoma cells include cells with a high nucleus to cytoplasm (N/C) ratio and cells that are enlarged and that the cells have a considerable dark appearance and identifying such abnormalities with a Papanicolau stain. (see entire document, e.g., page 27 and Figure 1).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to predictably substitute Papanicolau stain for the DAPI stain of Bubendorf et al to identify a high nucleus to cytoplasm (N/C) ratio and the other transitional cell carcinoma cell morphological abnormalities taught in the art such as an enlarged nucleus, a considerable dark appearance of a cell or an irregular nuclear border which can be visualized with Papanicolau stain as compared to a transitional epithelial cell with a normal morphology as taught by Brown, Skacel and Bubendorf, to identify single cells with morphological abnormalities, then destain the Papincolaou stain and then further analyze the same single cells using the FISH stains of Bubendorf et al and Skacel et al to identify the same single cells as transitional cell carcinoma cells and diagnose bladder cancer in view of these references as a whole.

In this case, one of skill in the art would have appreciated that there are multiple art-recognized morphological abnormalities and multiple art-recognized stains that can identify the known morphological abnormalities of transitional cell carcinoma cells in voided urine samples and would have considered such art-recognized staining and destaining techniques and visualizing known morphological abnormalities as obvious variants of each other which can be predictably substituted one for the other in methods of identifying transitional cell carcinoma cells and/or monitored together to identify the same single cells as transitional cell carcinoma cells. Furthermore, because these stains and morphological abnormalities were all known in the art to identify transitional cells as transitional cell carcinoma cells and because methods of destaining slides stained with Papanicolau stain and then using FISH stains on the same cells were known in the art and because methods of imaging the same single cells were known in the art, one of skill in the art clearly would have a reasonable expectation of success in identifying transitional cell carcinoma cells from a voided urine sample, by such

methods, in view of the references. Notably, as Skacel et al teach that the slides must be destained after staining with Papincolaou before using FISH and marking the areas of the slide containing the abnormal cells (see page 382, right column), it is submitted that one of skill in the art would have recognized that Papincolaou stain would need to be destained before using a FISH stain and that the same single cells could be visualized to confirm their identity as transitional cell carcinoma cells. Furthermore, Skacel et al teach that there are sensitivity limitations of using voided urine cytology and that adjuncts to urine cytology have been sought, such as FISH assays (see page 382, left column), so it is submitted one of skill in the art would have recognized that there would be an advantage, i.e., increased sensitivity and specificity in detecting transitional cell carcinoma cells by combining voided urine Papincolau cytology staining and FISH staining on the same cells to identify single cells that have both morphological abnormalities and chromosomal abnormalities as taught in the art.

Finally, with respect to claim 93, Bubendorf et al teach that the samples should be cytospun onto slides at a cell density between 100 to 400 per field and optimizing the density to 100 to 200 cells per visual filed if more than 4000 cells were in a field (see page 80, left column). Accordingly, it is submitted that the prior art recognized that the cell density of cells on the cytospin slide was to be optimized and could be optimized by routine experimentation, such that a step of cytospinning the cells in a sample to a density of 300-500 cells per square mm would not have been considered inventive by one of skill in the art. Furthermore, the Office does not have the resources for determining the actual cell density per square mm in the slides taught by Bubendorf and it is noted that cell density is dependent upon the amount of cells in the original sample and the amount of sample loaded for cytospinning, such that any slides prepared would have a variety of cell densities depending on the amount of cells in the voided urine sample. Furthermore, as such cytospinning methods were commonly practiced in the art and because there is an unknown random amount of cells in the original sample some slides prepared by the methods of Bubendorf would also randomly have a density of 300-500 cells per square mm, absent a showing otherwise. For these reasons, cytospinning the samples to a density of 300-500 cells per square mm is also

considered to be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

7. Claim 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bubendorf et al (Am J Clin Pathol., 116:79-86, 2001, of record) in view of Skacel et al (Anal Quant Cytol Histol, 23(6): 381-387, 2001, of record) and in view of Brown (Urol. Clin. NA., 27(1):25-37, 2000, of record), as applied to Claims 72, 73, 82, 87, 89, 91 and 93 above, and further in view of US Patent 6,418,236 (Ellis et al, July 9, 2002, of record) **or** Kaplinsky (43rd ASH Annual Meeting, Blood, 98(Part 2):348b, 2001, IDS filed 4/9/08).

Claim 84 is further drawn herein to said imaging being effected using an automated cell imaging device capable of at least dual imaging.

Bubendorf et al in view of Skacel et al and in view of Brown teach and render obvious methods as set forth in the above rejection of claims under 35 U.S.C. 103(a).

These references do not expressly teach imaging cells with an automated imaging device capable of dual imaging.

This deficiency is made up for in the teachings of US Patent 6,418,236 or Kaplinsky. US Patent 6,418,236 teaches automated image analysis using a microscope capable of dual imaging to image cells stained with two stains, such as morphological stains and in situ hybridization stains which can be fluorescent stains (see entire document, e.g., column 1, lines 26-59, column 4, lines 31-67, column 5, lines 1-15).

Kaplinsky teaches automated image analysis using a microscope capable of dual imaging to image the same cells stained with a morphological stain and fluorescent in situ hybridization (FISH) stains (see entire document, e.g., abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify transitional cell carcinoma cells from a voided urine sample using the processes rendered obvious by Bubendorf et al in view of

Skacel et al and in view of Brown and additionally imaging the stained cells with an automated microscope capable of dual imaging to identify the same single cells as transitional cell carcinoma cells.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to identify transitional cell carcinoma cells by such processes because the stains and processes of Bubendorf et al and Brown were known in the art to identify transitional cell carcinoma cells while the automated imaging microscope of US Patent 6,418,236 would allow for faster processing of samples. For example, US Patent 6,418,236 teaches that automated imaging analysis "eliminates the need for operator input to locate biological objects or areas of interest for analysis" (see column 8, lines 30-32). Additionally, Kaplinsky teaches that automated imaging analysis "provides two important features: scanning large number of cells, and performing combined analysis of morphology and FISH on the same cells" (see abstract, lines 6-8). Thus, there would be an advantage and a reasonable expectation of success in identifying transitional cell carcinoma cells from a voided urine sample by additionally imaging the stained cells with an automated microscope capable of dual imaging as taught by US Patent 6,418,236 or Kaplinsky to identify the same single cells as transitional cell carcinoma cells, in view of the references.

For these reasons, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR

1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ishiwata et al (Urol., 57:811-815, 2001) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with morphological stains and FISH stains. Haferlach et al (Blood, 6:2459-2463, 1996) teach methods of visualizing stains in the same single cells stained with Giemsa and FISH stains. Placer et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with standard Papanicolau stain and FISH stains. Halling et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with FISH stains. Inoue et al (of record) teach methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer in the same single cells obtained from a urine sample wherein the cells are stained with Giemsa and FISH chromosome 9 stains. Darzynkiewicz et al (of record) discloses an automated cell-imaging device capable of dual imaging. Shimoni et al (of record) discloses an automated cell-imaging device capable of dual imaging of cells stained with a May-Grunwald-Giemsa stain and FISH probes. Boon et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with a Giemsa stain or a Papanicolau stain. Otto et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with a Hematoxylin stain and an Eosin stain. US Patents 6,174,681 (2001), 6,376,188 (2002) and

7,232,655 (2007) (all Halling et al) disclose a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in the same single cells stained with a morphological stain, such as DAPI and FISH stains. Dalquen et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with standard Papanicolau stain or FISH stains. Sokolova et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in the same single cells stained with DAPI and FISH stains. Mezzelani et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in the same single cells stained with DAPI and FISH stains.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Thursday, 6:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy

571-272-9935

/bd/
Examiner, Art Unit 1643
December 21, 2011

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1642